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(54) Tetracycline dosage form.

(57) The present invention relates to a pharmaceutical composition and a method for preparing same.

There is a high incidence of gastrointestinal side effects associated with a number of antibiotics and provision of an enteric coating to reduce side effects may also prevent adequate absorption of the antibiotic.

It is an object of the present invention to overcome, or at least alleviate these difficulties.

The present invention provides a pharmaceutical composition including a core element including at least one active ingredient including at least one tetracycline antibiotic; and a core coating for the core element which is partially soluble at an acidic pH. In use, a dissolution profile is generated for the pellet composition which is equal to or greater than the minimum dissolution profile required to provide bioequivalence with a capsule or tablet containing an equal amount of the active ingredient in an uncoated form.

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TETRACYCLINE DOSAGE FORM

The present invention relates to a pharmaceutical composition, in particular a pharmaceutical composition including an antibiotic agent and a method for preparing same.

It is known in the prior art that there is a high incidence of gastrointestinal side effects associated with a number of known antibiotics including tetracycline antibiotics. These side effects include nausea and dyspepsia, particularly when taken on an empty stomach. Other side effects include reaction of the central nervous system leading to ataxia, lightheadedness, dizziness or vertigo. Whilst it is known in the prior art to provide an enteric coating to reduce side effects by avoiding dissolution in the stomach, such enteric coatings may also prevent adequate absorption of the antibiotic. Accordingly a product offering at least partial protection against these adverse reactions would have definite advantages over all the rest of the drug products in this group.

Accordingly, it is an object of the present invention to overcome, or at least alleviate, one of more of the difficulties related to the prior art.

Accordingly in a first aspect according to the present invention there is provided
a pharmaceutical composition including
a core element including at least one active ingredient including at least one tetracycline antibiotic; and
a core coating for the core element which is partially soluble at an acidic pH and which, in use, generates a dissolution profile for the pellet composition which is equal to or greater than the minimum dissolution profile required to provide bioequivalence with a capsule or tablet containing an equal amount of the at least one active ingredient in an uncoated form.

A first dissolution profile may be measured at a pH level approximating that of the stomach. At least a second dissolution profile may be measured at pH levels approximating that of at least one point in the small intestine. An acidic pH may simulate the stomach and a less acidic to basic pH may simulate the small intestine.

By "acidic pH" as used herein we mean a pH in the range of approximately 1 to 4. By "less acidic to basic pH" as used herein we mean a pH in the range of approximately 4.5 to 7.5.

A pH of approximately 1.2 may be used to simulate the pH of the stomach.

A pH of approximately 5.0 to 6.0 preferably 5.5 may be used to simulate the pH at the upper end of the small intestine.

"Bio-equivalence" as used herein, means that the area under the curve (AUC) and the maximum concentration in the blood (Cmax) from a plot of blood concentration of active ingredient versus time are within certain designated requirements by Health Authorities. For example the blood drug concentrations achieved may be plus or minus 20% in 80% or above of the subject when compared to an immediate release product.

"Dissolution profile" as used herein, means a plot of percentage of active ingredient released as a function of time. The dissolution profile may be measured utilising the standard test USPXXI 1958 and the 3rd and 5th Supplements. (Test 711). A profile is characterised by the test conditions selected. Thus the dissolution profile may be generated at a preselected shaft speed and pH of the dissolution media.

Preferably the pharmaceutical pellet composition generates a dissolution profile in which greater than 10% dissolved in one hour at pH 1.2 and greater than 50% dissolved after 30 minutes at pH 5.5.

More preferably the dissolution profile is preferably 20-75% dissolved in 20 minutes and/or 50% or greater dissolved in one hour at pH 1.2, and greater than 75% dissolved after 30 minutes at pH 5.5.

In order to avoid toxicity and/or other side effects, the dissolution profile at pH 1.2 should preferably not extend beyond that defined by the following table:-

fillers may be selected from mannitol, sucrose, lactose, dextros , sodium chloride, sorbitol and mixtures thereof. Lactose and/or starch fillers are prepared where the core element is in a tablet form.

The lubricant and disintegrant, where present, may be selected from any of these known per se in the formulation of tablets. As lubricant, talc, magnesium stearate or stearic acid may be used. As disintegrant, microcrystalline cellulose or polacrillin potassium may be used.

In a further preferred aspect, the core element according to this aspect of the present invention may further include other carriers or excipients, stabilizing agents, solution accelerants, and colorants.

A solution accelerator may be included. A polyethylene glycol may be used as a solution accelerator. The preferred polyethylene glycol used may be selected from polyethylene glycol 4000 and polyethylene glycol 6000.

The filler may be present in amounts of from approximately 0 to 75% by weight, preferably 1 to 40% by weight, based on the total weight of the core element. The polyethylene glycol component when present may be present in amounts of from approximately 1 to 50% by weight based on the total weight of the core element.

Typical core formulations may be prepared in the amounts as follows:

Spheronisation process		
Example A		
(antibiotic)	minocycline powder	20 - 74%
	sugar seeds	25 - 80%
(binder)	hydroxypropyl methylcellulose (as hydroxypropyl/methanol granulating solution)	0.1 - 20%
Example B		
(antibiotic)	minocycline powder	20 - 74%
	sugar seeds	25 - 80%
(binder)	povidone (as povidone/ethanol granulating solution)	0.1 - 20%

Extrusion process		
(antibiotic)	minocycline powder	20 - 74%
(filler)	microcrystalline cellulose	1 - 75%
(binder)	Hydroxypropyl cellulose	1.0 - 10%
(solvent)	Water	sufficient for extrusion

Tablet Form		
(antibiotic)	minocycline powder	20 - 74%
(filler)	lactose	1 - 40%
(lubricant)	talc	1 - 40%
(disintegrant)	microcrystalline cellulose	1 - 75%

The pharmaceutical composition according to this aspect of the present invention further includes a hybrid core coating. It will be understood that the hybrid core coating reduces but does not eliminate dissolution in the acidic environment of the stomach but which will rapidly dissolve in the environment of the upper intestinal tract.

The enteric polymer, whilst substantially insoluble at acidic pH may dissolve rapidly in the less acidic to basic pH encountered in the small intestine.

The at least partially acid soluble component may dissolve rapidly in the acid environment of the

stomach.

Preferably the hybrid core coating includes approximately 15 to 85% by weight, based on the total weight of th hybrid core coating, excluding filler, of at least one acid insoluble polymer and may be selected from the enteric polymers cellulose acetate phthalate, hydroxypropyl methylcellulose phthalate, polyvinyl acetate phthalate, methacrylic acid copolymer type A, methacrylic acid: acrylic acid methyl ester copolymer, hydroxypropyl methylcellulose acetate succinate, shellac, cellulose acetate trimellitate or mixtures thereof; and

approximately 1 to 60% by weight, based on the total weight of the hybrid core coating, excluding filler, of an at least partially acid soluble component selected from polyvinylpyrrolidone, hydroxypropyl cellulose, hydroxypropyl methylcellulose, methyl cellulose, sugars and mixtures thereof.

The hybrid core coating may further include

at least one plasticiser;

and optionally

at least one filler.

The at least one plasticiser may be selected from diethyl phthalate, triethyl citrate, triethyl acetyl citrate, triacetin, tributyl citrate, polyethylene glycol, glycerol and the like. It will be understood that the plasticiser used may be largely dictated by the polymer used in the coating formulation.

The plasticiser may be present in any suitable effective amount. Amounts of from 0 to approximately 50% by weight preferably 1-30% by weight based on the total weight of the hybrid core coating have been found to be suitable.

It should be noted that plasticisers which are significantly water soluble may behave as a partially acid soluble component in the hybrid core coating.

A preferred hybrid core coating includes		
(enteric polymer)	hydroxypropyl methyl cellulose phthalate	50-80%
(acid-soluble polymer)	polyvinylpyrrolidone	10-40%
(plasticiser)	triethyl citrate	1-30%

As stated above the hybrid core coating may further include at least one filler. The at least one filler may be selected from those insoluble fillers listed above for the manufacture of the core element.

The filler may be present in any suitable effective amount. Amounts of from 0 to approximately 75% by weight, preferably 0-50% by weight based on the total weight of the core coating have been found to be suitable.

A hybrid core coating composition may be provided in the form of a solution, dispersion or suspension.

The solvent may be present in amounts of from approximately 25 to 97% by weight based on the total weight of the hybrid core coating composition. The solvent for the enteric polymer may be an aqueous solvent. The solvent for the enteric polymer may be selected from water, methanol, ethanol, methylene chloride and mixtures thereof.

Typical compositions of hybrid core coatings (following evaporation of the levels of the solvent) are:

		% coat weight
A.	insoluble at pH 1.2 (enteric)	30 - 80
	acid soluble	10 - 60
	plasticiser	1 - 30
	Solvent of hybrid core coating solution	85 - 97%
B.	For aqueous redispersion polymers of an enteric nature, formulation A above becomes:	
	insoluble polymer at pH 1.2 (enteric)	30 - 80
	acid soluble	10 - 60
	plasticiser	1 - 30
	Solvent (water) is of the hybrid core coating solution	75 - 97%
Sufficient plasticiser is added to ensure film formation.		

In a further aspect of the present invention there is provided a method for preparing a core element which method includes

providing an active ingredient including
at least one tetracycline antibiotic;
at least one core seed; and
at least one binding agent; and
coating the core seeds with the active ingredient and binding agent

In a preferred form the at least one binding agent is provided in a granulating solution. In this form the coating step may be conducted as a spheronisation process. The spheronisation process includes contacting the cores seeds with the active ingredient and simultaneously adding the granulating solution thereto. The spheronisation process may be conducted in a spheronising machine.

In an alternative aspect of the present invention the method according to the present invention may further include providing the active ingredient and binder in a solution or slurry of a solvent and spraying the core seeds with the solution or slurry. The spraying step may be conducted in a fluidised bed chamber.

In a further alternative aspect of the present invention, the method for preparing a core element may include providing
at least one tetracycline antibiotic,
at least one binding agent, and
an effective amount of a solvent;
mixing the ingredients;
and subjecting the ingredients to an extrusion step, followed by marumerisation in a marumeriser.

The solvent may be an aqueous or organic solvent or mixtures thereof. The solvent may be present in an amount effective to allow the ingredients to be extruded.

The core elements formed may then be subjected to a drying step. The drying step may be conducted in a fluidised bed or drying oven.

In a still further aspect of the present invention there is provided a method for preparing a pharmaceutical pellet composition as described above which method includes
providing a hybrid core coating composition including a solution or dispersion of
at least one polymer which is substantially insoluble at an acidic pH but at least partially soluble at a less acidic to basic pH;
at least one component which is at least partially soluble at an acidic pH;
and a fluidized bed reactor;
introducing the core element into the fluidized bed reactor; and
Spray coating of pellets may be undertaken utilising bottom or top located spray nozzles. A bottom spray nozzle may reside proximate the base of the fluidising bed facing upwards while a top spraying nozzle is located above the contents of the bed and facing downwards.

In a still further alternative aspect of the present invention, the method for preparing a core element may include
providing
at least one tetracycline antibiotic;
at least one lubricant;
at least one filler; and
at least one disintegrant;
mixing the ingredients; and
subjecting the ingredients to a direct compression step.

In a still further aspect of the present invention, there is provided a method for preparing a coated tablet as described above, which method includes
providing a hybrid core coating composition, including a solution or dispersion of
at least one polymer which is substantially insoluble at an acidic pH but at least partially soluble at a less acidic pH;
at least one component which is at least partially soluble at an acidic pH;
and a pan coater;
introducing the tablets into the pan coater; and
spraying or pouring the hybrid core coating into the pan to coat the tablets.

The pharmaceutical pellet or tablet composition may be administered under a similar dosage regimen to that used in the prior art. For minocycline, for example the multi-pellet encapsulated or tablet form may be administered at the same frequency as commercially available forms such as that sold under the trade designation Minocin, e.g. 200 mg followed by 100 mg every 12 hours.

In accordance with a further aspect of the present invention there is provided a method of treating bacterial inf ctions in patients requiring such treatment which method includes administering to a patient an

effective amount of a pharmaceutical p llet composition as d scribed above.

It will be understood that the method of treating bacterial infections according to this aspect of the present invention may provide an advantage in reduced sid effects associated with prior art antibiotics as described above. These side effects include nausea, dyspepsia and central nervous system irregularities.

The present invention will now be more fully described with r ference to the accompanying examples. It should be understood however that the following description is illustrative only and should not be taken in any way as a restriction on the generality of the invention specified above.

EXAMPLE 1

Pellet compositions A and B having the formulations set out below were prepared as described below.

A		
Core Composition		
Non pareil seed cores	:	150 mg
Minocycline hydrochloride	:	123 mg
Povidone USP	:	20 mg
Hybrid Core Coating Composition		
Hydroxypropyl methylcellulose phthalate	:	30 mg
Diethyl phthalate	:	2.5 mg
B		
Core Composition	:	
Non pareil seed cores	:	150 mg
Minocycline hydrochloride	:	123 mg
Povidone USP	:	20 mg
Hydroxypropyl methylcellulose phthalate	:	6 mg
Diethyl phthalate	:	1.5 mg
Hydroxypropyl methylcellulose	:	1.5 mg

The sugar seeds were placed in a spheroniser and coated with a dry mixture of the active ingredients and inactive excipients whilst concomittantly adding a solution of the binder components.

The wet cores so formed were then placed in a fluidised bed dryer for 1 hour and placed in a bottom spray coating fluidised bed apparatus. The hybrid core coating composition was then delivered into the fluidised bed via the bottom spraying nozzle.

The wet pellets so formed were then allowed to dry.

Example 2

A dissolution test was conducted on the pellet compositions A and B and on commercial tetracycline capsules, for comparison purposes, utilising the test method USPXXI 1985 and the 3rd and 5th Supplement thereto. (Test 711). The commercial tetracycline capsules these incorporating minocycline powders and sold under the trade designation "Minocin". A sample is dissolved in an aqueous medium previously degassed and equilibrated to 37° C. The media are USP pH 1.2 media without enzymes or pH 5.5 phthalate buffer. A sample of known volume is withdrawn at designated time intervals from the bath as directed and subjected to a suitable assay procedure. The mg of minocycline released as a function of time is plotted as the dissolution profile.

The tests were conducted at pH 1.2 and pH 5.5.

The baskets containing the samples were rotated at approximately 50 r.p.m. and the aqueous medium maintained at approximately 37° C.

The results are given in Tables 1 and 2 and Figures 1 and 2 herein. The hybrid coating on pellet

composition A functioned as an enteric coating and no dissolution at pH 1.2 was observed over a 1 hour period.

TABLE 1

DISSOLUTION DATA FOR PELLET COMPOSITION A MEASURED AT pH 5.5 (Averaged data for 3 samples)				
TIME (MIN)	AMOUNT RELEASED (mg)	(STD DEV)	% RELEASED	(STD DEV)
10	27.18	(1.07)	82.17	(4.06)
20	32.79	(0.83)	99.12	(0.38)
30	33.35	(1.02)	100.78	(1.49)
40	33.29	(1.06)	100.61	(1.56)

TABLE 2

DISSOLUTION DATA FOR PELLET COMPOSITION B MEASURED AT pH 1.2 (Averaged data for 3 samples)				
TIME (MIN)	AMOUNT RELEASED (mg)	(STD DEV)	% RELEASED	(STD DEV)
10	7.97	(0.32)	15.60	(0.64)
20	17.78	(0.75)	34.71	(1.62)
30	28.17	(0.89)	51.23	(2.15)
40	33.10	(1.10)	64.79	(2.66)
50	38.65	(1.23)	75.67	(3.09)
60	42.45	(1.24)	83.09	(3.13)

TABLE 3

DISSOLUTION DATA FOR PELLET COMPOSITION B MEASURED AT pH 5.5 (Averaged data for 3 samples)				
TIME (MIN)	AMOUNT RELEASED (mg)	(STD DEV)	% RELEASED	(STD DEV)
10	45.27	(2.30)	88.60	(4.87)
20	50.25	(0.49)	98.33	(1.66)
30	50.91	(0.17)	99.64	(1.01)
40	51.02	(0.05)	99.85	(0.93)
50	50.89	(0.21)	99.58	(1.03)
60	51.00	(0.31)	99.80	(1.08)

TABLE 4

DISSOLUTION DATA FOR MINOCIN® i.e. MINOCYCLINE POWDER CAPSULES MEASURED AT pH 1.2 (Averaged data for 6 samples)				
TIME (MIN)	AMOUNT RELEASED (mg)	(STD DEV)	% RELEASED	(STD DEV)
5	16.84	(3.80)	16.24	(3.71)
15	101.79	(4.60)	98.16	(4.38)
20	103.94	(3.48)	100.23	(3.10)
30	105.47	(1.92)	101.71	(1.67)
40	105.75	(1.53)	101.98	(1.34)
60	106.41	(1.14)	102.62	(1.33)

TABLE 5

DISSOLUTION DATA FOR MINOCIN® i.e. MINOCYCLINE POWDER CAPSULES MEASURED AT pH 5.5 (Averaged data for 8 samples)				
TIME (MIN)	AMOUNT RELEASED (mg)	(STD DEV)	% RELEASED	(STD DEV)
5	7.87	(4.60)	7.43	(4.45)
10	55.14	(8.67)	53.48	(8.38)
15	80.70	(8.32)	78.25	(8.07)
30	96.06	(4.44)	93.14	(4.29)
40	99.07	(1.83)	96.06	(1.77)
50	100.22	(1.39)	97.18	(1.33)
60	100.59	(1.23)	97.54	(1.16)
STD DEV = Standard Deviation				

EXAMPLE 3

Clinical Trials

For the initial trial in man, Pellet Compositions A and B were formulated to provide information on absorption site.

To this end, Pellet Composition A was formulated not to dissolve in the stomach and to dissolve exceedingly fast in the small intestine.

Pellet Composition B was formulated to control the dissolution of minocycline in the stomach. The controlled dissolution in the stomach meant that minocycline would appear in the region immediately after the pyloric sphincter wherein the pH is normally somewhere between 1.2 and 5.5. A pH of 1.2 has been selected to simulate the pH of the fasted stomach. The dissolution at or after pH 5.5 was substantially similar to that measured for Pellet Composition A.

Test Results in Man

The bioavailability of compositions A and B were compared to that of capsules of Minocycline

hydrochloride formulated in a powder; (Minocycline hydrochloride powder is extremely soluble under acidic conditions).

Composition B mor closely approached the bioavailability of Minocyclin hydrochloride capsules.

Regulatory authorities assess products by comparing bioequivalences - the same rate and extent of absorption as a reference product. Thus, for extent the test product must not be less than 80% of the product.

SUMMARY

A single dose, balanced, three-way crossover study involving 18 healthy, adult volunteers (6 female, 12 male) compared the bioavailability of minocycline in three formulations administered in the fasting state.

The two test products were Pellet composition A capsules and B capsules, containing modified-release pellets of minocycline hydrochloride equivalent to 100 mg minocycline base and preferred as described above. The reference product was Lederle Minomycin® capsules containing minocycline hydrochloride equivalent to 100 mg minocycline base.

The study was divided into three periods with a one week interval separating each period. Subjects were randomised by weight into three equal groups which were then randomly assigned to either dosage regimen A, B or C. Dosing regimen sequence followed a three by three Latin Square design where three regimen sequences were employed. The dosing regimens A, B and C were as follows.

Regimen A:

(2 x 100 mg) A capsules were administered as a single oral dose with 180 mL of water following a 12 hour overnight fast.

Regimen B:

(2 x 100 mg) B capsules were administered as a single oral dose with 180 mL of water following a 12 hour overnight fast.

Regimen C:

(2 x 100 mg) Minomycin® capsules were administered as a single oral dose with 180 mL of water following a 12 hour overnight fast.

For regimens A, B and C, blood samples (6 mL) were collected from an indwelling venous catheter at 0, 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 6.0, 8.0, 10.0 and 12.0 hours following administration of the dose. Further blood samples were collected by venipuncture technique at 24.0, 28.0, 32.0, 34.0 and 48.0 hours after the dose.

In view of the unexplained, aberrant nature of the bioavailability data for subject 5, his data were excluded from the statistical analyses and only data from the remaining 17 subjects are discussed.

Examination of the AUC data (refer Tables 6) indicates only a small but important difference between the two test formulations (A and B capsules). Both of these products had significantly lower bioavailability relative to the reference product, (Minomycin® capsules). The mean relative bioavailability value for A capsules was 82.8 ± 13.5% while for B capsules the extent of absorption was 88.3 ± 8.1%.

Although the reference product produced significantly higher mean C_{max} values of minocycline than the test product, (A capsules), there was no statistically significant difference between the mean C_{max} values observed for B capsules and the reference product.

There was no significant difference in the mean t_{max} values for the three products tested even though A capsules showed lag times of up to 2 hours in some subjects.

The mean elimination half lives calculated from log linear regression of the terminal concentration time data were not significantly different for each treatment. The half life values obtained are compatible with values reported for minocycline in the literature.

Thus the test product, B capsules, is the preferred formulation since it does not show a lag time and

demonstrates a slightly higher, but not statistically significant, mean relative bioavailability and mean maximum observed concentration value than A capsules.

TABLE 6

MEAN (+ SD) PHARMACOKINETIC PARAMETERS N = 17				
PARAMETERS	REGIMENS			STATISTICAL ANALYSIS
	A	B	C	
	Composition A fasting	Composition B fasting	Minomycin® fasting	Significance level p 0.05
F% Relative Bioavailability	82.8 (13.5)[a]	88.3 (8.1)	-	student's paired t-test NOT SIGNIFICANT A = B
$AUC_{0-\infty}$ (mg.h/L)	50.32 (8.84)	54.28 (9.74)	61.80 (10.69)	ANOVA SIGNIFICANT A = B, A C, B C[b]
C_{max} (mg/L)	2.93 (0.78)	3.08 (0.88)	3.68 (0.95)	ANOVA SIGNIFICANT A = B, A C, B = C
t_{max} (h)	3.13 (0.69)	2.62 (1.05)	2.44 (1.13)	ANOVA NOT SIGNIFICANT
$t_{1/2}$ (h)	4.83 (2.09)	14.92) (2.20)	15.72 (2.39)	ANOVA NOT SIGNIFICANT
Ke (h^{-1})	0.0476 (0.007)	0.0474 (0.007)	0.0450 (0.007)	ANOVA NOT SIGNIFICANT

a standard deviation
b Scheffe's F-test for significance
Composition A capsules show lag times from 0 to 2 hours.

Composition B capsules do not show a lag time.

$AUC_{0-\infty}$(mg.h/L) = Area under the curve to infinite time, calculated using trapezoidal rule from 0 hours to the last measurable concentration and extrapolated to infinite time by the addition of the quantity: last measured concentration divided by the elimination rate constant.

Ke(h^{-1}) = Elimination rate constant: Apparent first order elimination rate constant calculated as the slope of a log-linear regression line fitted to at least the last four measured data points of the serum concentration versus time profiles.

$t_{1/2}$(h) = Elimination half life: 0.693/elimination rate constant.

C_{max}(mg/L) = Maximum observed serum concentration was obtained from visual inspection of the serum concentration versus time points.

t_{max}(h) = Time to reach maximum observed serum concentration was obtained from visual inspection of the serum concentration versus time data points.

F% = Relative bioavailability value shown as a percent.

$$\frac{AUC_{0-\infty}(test)}{AUC_{0-\infty}(ref.)} \times \frac{Dose\ (ref.)}{Dose\ (test)} \times 100$$

The dissolution profile generated for pellet composition A may be viewed as slightly below the minimum dissolution required to provide substantial bioequivalence with the reference product (Minomycin® capsules).

The dissolution profile generated for pellet composition B may be viewed as slightly above the minimum dissolution required to provide substantial bioequivalence with the reference product (Minomycin® capsules).

The composition of the core coating may accordingly be modified slightly between that of A or B in

order to define the minimum dissolution profile for the pharmaceutical pellet composition according to the present invention in the manner discussed above. The amount of the at least partially insoluble component and/or the insoluble component may be increased to improve bioequivalence with Minomycin for example. Th composition of the core coating may be modified further to improve the bioequivalence with the reference product.

Finally, it is to be understood that various other modifications and/or alterations may be made without departing from the spirit of the present invention as outlined herein.

Claims

1. A pharmaceutical composition including
a core element including at least one active ingredient including at least one tetracycline antibiotic; and
a core coating for the core element which is partially soluble at an acidic pH and which, in use, generates a dissolution profile for the pellet composition which is equal to or greater than the minimum dissolution profile required to provide bioequivalence with a capsule or tablet containing an equal amount of the at least one active ingredient in an uncoated form.

2. A pharmaceutical composition according to claim 1 wherein the at least one tetracycline antibiotic is selected from tetracycline, chlortetracycline, demeclocycline, methacycline, oxytetracycline, minocycline and mixtures thereof.

3. A pharmaceutical composition according to claim 1 wherein a first dissolution profile is measured at a pH level approximating that of the stomach and a second dissolution profile is measured at a pH level approximately that of at least one point in the small intestine;
the first and second dissolution profiles for the pharmaceutical composition each being equal to or greater than the minimum dissolution required to provide substantial bioequivalence with a capsule or tablet containing the at least one active ingredient in an uncoated form.

4. A pharmaceutical composition according to claim 2 wherein the pellet composition generates a total dissolution, in use a total dissolution of greater than 10% dissolved in one hour at pH 1.2 and greater than 50% dissolved after 30 minutes at pH 5.5.

5. A pharmaceutical composition including
a core element including at least one active ingredient including at least one tetracycline antibiotic; and
a core coating for the core element which is partially soluble at an acidic pH;
and wherein the active ingredient is available for substantially complete absorption substantially immediately after entering the small intestine.

6. A pharmaceutical composition according to claim 5 wherein the core coating is a hybrid core coating which coating provides a controlled low rate of release at an acidic pH and allows a more rapid rate of release at a less acidic to basic pH.

7. A pharmaceutical composition according to claim 6 wherein the hybrid core coating includes
at least one polymer which is substantially insoluble at an acidic pH and at least partially soluble at a less acidic to basic pH;
at least one component which is at least partially soluble at an acidic pH.

8. A pharmaceutical composition according to claim 7 wherein the tetracycline antibiotic is selected from tetracycline, chlortetracycline, demeclocyline, methacycline, oxytetracycline, minocycline and mixtures thereof.

9. A pharmaceutical composition according to claim 7 wherein the core element is a pellet, tabletted pellet or tablet.

10. A pharmaceutical composition according to claim 8 wherein the tetracycline antibiotic includes minocycline.

11. A pharmaceutical composition according to claim 7 wherein the core element includes an effective amount of
at least one tetracycline antibiotic;
at least one core seed; and
at least one binding agent.

12. A pharmaceutical composition according to claim 7 wherein the core element includes an effective amount of
at least one tetracycline antibiotic;
at least one binding agent;
and at least one filler.

13. A pharmaceutical composition according to claim 7 wherein the core element includes
at least one tetracycline antibiotic;
at least one lubricant; and
at least one filler.

14. A pharmaceutical composition according to claim 11 wherein the at least one tetracycline antibiotic is present in amounts of approximately 5 to 95% by weight based on the total weight of the core element; and
the at least one core seed is present in amounts of from approximately 5.0 to 25% by weight based on the total weight of the core element.

15. A pharmaceutical composition according to claim 14 wherein the core element has a formulation:

minocycline powder	25 - 94%
sugar seeds	5 - 74%
hydroxypropyl cellulose	0.1 - 20%

16. A pharmaceutical composition according to claim 14 wherein the core element has a formulation:

minocycline powder	25 - 94%
sugar seeds	5 - 74%
povidone	0.1 - 20%

17. A pharmaceutical composition according to claim 12 wherein the core element has a formulation:

minocycline powder	25 - 94%
microcystalline cellulose	1 - 40%
Hydroxypropyl cellulose	1.0 - 10%

18. A pharmaceutical pellet composition according to claim 7 wherein the hybrid core coating includes approximately 15 to 85% by weight, based on the total weight of the hybrid core coating, excluding filler, of at least one acid insoluble polymer selected from cellulose acetate phthalate, hydroxypropyl methylcellulose phthalate, polyvinyl acetate phthalate, methacrylic acid copolymer type A, methacrylic acid: acrylic acid methyl ester copolymer, hydroxypropyl
methylcellulose acetate succinate, shellac, cellulose acetate trimellitate or mixtures thereof; and
approximately 1 to 50% by weight, based on the total weight of the hybrid core coating, excluding filler, of an at least partially acid soluble component selected from polyvinylpyrrolidine, hydroxypropyl cellulose, hydroxypropyl methyl cellulose, methyl cellulose, sugars and mixtures thereof.

19. A pharmaceutical composition according to claim 18 wherein the hybrid core coating further includes
0 to approximately 50% by weight based on the total weight of the hybrid core coating, excluding filler, of a plasticizer at least one plasticizer selected from diethyl phthalate, triethyl citrate, triethyl acetyl citrate, triacetine, tributyl citrate, polyethylene glycol and glycerol; and
0 to approximately 50% by weight based on the total weight of the hybrid core coating of at least one filler selected from silicon dioxide, talc, alumina, starch, calcium, potassium, powdered cellulose, microcrystalline cellulose and mixtures thereon.

20. A pharmaceutical composition according to claim 19 wherein the hybrid core coating has a formulation:

hydroxypropyl methyl cellulose phthalate	50 - 80%
polyvinylpyrrolidone	10 - 40%
diethyl phthalate	1 - 30%

21. A pharmaceutical product including a plurality of pellets including
a core element including at least one active ingredient including at least one tetracycline antibiotic;
a core coating for the core element which is partially soluble at an acidic pH and which, in us , generates a dissolution profile for the pellet composition which is equal to or greater than the minimum dissolution profile required to provide substantial bioequivalence with a capsule or tablet containing an equal amount of the at least one active ingredient in an uncoated form.

22. A method for preparing a pharmaceutical composition which method includes
providing
at least one active ingredient including at least one tetracycline antibiotic;
at least one core seed;
at least one binding agent in a granulating solution; and
contacting the core seed with the active ingredient and simultaneously adding the binding agent solution thereto in a spheronization process to form a core element.

23. A method according to claim 22 which method further includes
providing
a hybrid core coating composition including
a solution or dispersion of
at least one polymer which is substantially insoluble at an acidic pH and at least partially soluble of a less acidic to basic pH; and
at least one component which is at least partially soluble at an acidic pH; and
a fluidized bed reactor;
introducing the core element into the fluidized bed reactor; and
spraying the hybrid core coating composition onto the core element.

24. A method of treating bacterial infections in patients requiring such treatment which method includes administering to a patient an effective amount of a pharmaceutical composition including
a core element including at least one active ingredient including at least one tetracycline antibiotic; and
a core coating for the core element which is partially soluble at a highly acidic pH and which, in use, generates a dissolution profile for the pellet composition which is equal to or greater than the minimum dissolution required to provide substantial bioequivalence with a capsule or tablet containing the at least one active ingredient in an uncoated form.

25. A method according to claim 24 wherein the pharmaceutical composition includes
a core element including at least one active ingredient including at least one tetracycline antibiotic; and
a core coating for the core element which is partially soluble at acidic pH; and wherein the active ingredient is available for substantially complete absorption substantially immediately after entering the small intestine.

26. A method according to claim 25 wherein the at least one tetracycline antibiotic is selected from tetracycline, chlortetracycline, demeclocycline, methocycline, oxytetracycline, minocycline and mixtures thereof.

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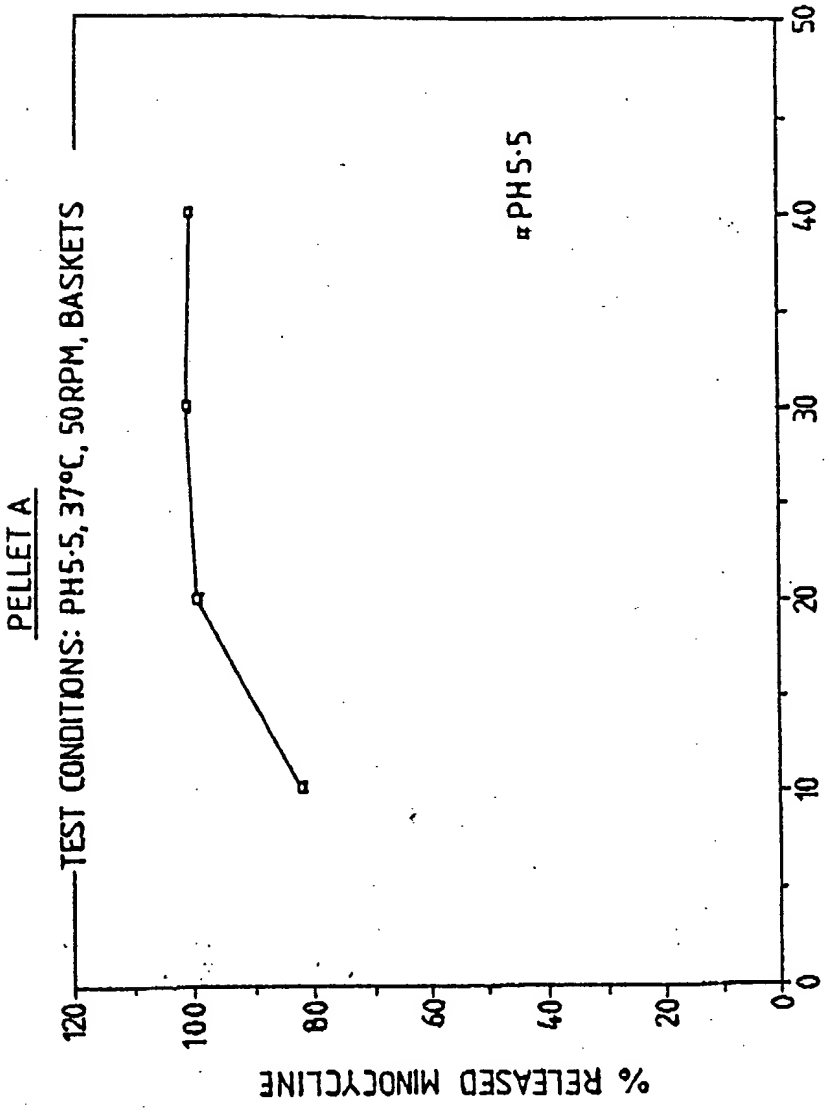

FIG 1